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(54) **Formulations and their use in the treatment of neurological diseases**

Zusammenfassungen und ihren Verwendung in der Behandlung von neurologischen Krankheiten

Formulations et leur utilisation dans le traitement de maladies neurologiques

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Description

[0001] This invention relates to preparations for use in the treatment of neurological diseases. More parcularly, the invention relates to preparations for the controlled administration of mono- or di-aminopyridine active agents and to the use of such preparations in the treatment of neurological diseases characterised by a slowing of nerve impulse transmission, more especially multiple sclerosis and Alzheimer's disease.

[0002] Multiple sclerosis (MS) is a degenerative and inflammatory neurological disease which affects the central nervous system, more specifically the myelin sheath. MS causes demyelination of nerve fibres resulting in short-circuiting of nerve impulses and thus a slowing or blocking of transmission along the nerve fibres, with associated disabling symptoms.

[0003] Alzheimer's disease is a major cause of dementia in the elderly. It may be described as a progressive pathological deterioration in personality, memory and intellect consistent with a generalised atrophy of corresponding brain centres. The emotional state, behaviour, cognitive function and thought processes of sufferers are all adversely affected. A minor disimprovement in memory which gradually becomes more apparent is the first indication of the onset of the disease.

[0004] The incidence of the condition is slightly less than 1% of the general population of the U.K. but rises to 5% in the over-65's and to 20% in the over-80's.

[0005] The biochemical basis and neuropathology of the disease are better understood than its aetiology. The possibility of a genetic link is being investigated, as are suggestions that aluminium is a causative factor.

[0006] Treatments available to date are of, at best, limited value and the progression of the disease is irreversible. Death normally occurs less than a decade after the illness first presents itself (Barker, S. and Branford, D.;Pharm. Journal Jan. 26, 1991, pp 116-118).

[0007] 4-Aminopyridine (4-AP) has been found to improve the conduction of nerve impulses, thereby, alleviating symptoms in MS patients. 4-AP has been found to slow the potassium ion flow in nerve impulse transmission and, thereby, is effective in restoring conduction in blocked demyelinated nerves. In clinical trials carried out by Davis, F.A. and Stefoski, D. of The Rush Multiple Sclerosis Centre, U.S.A., 4-AP has been administered orally in multiple daily doses over 2-5 days to MS patients with mild to marked improvements being noted and minimal side effects.

[0008] 3,4-Di-aminopyridine (3,4-DAP) has also been found to improve specific neurological deficits and visual evoked response latencies in MS patients when administered orally in multiple daily doses. Bever, C.T. JR; Leslie, J.; Camenga, D.L.; Panitch, H.S.; and Johnson, K.P., Ann. Neurol. 27(4), pp. 421-427 (Apr. 1990).

[0009] 4-AP has also been found to improve the mental functions in patients with Alzheimer's disease. This effect is believed to be related to the potassium channel blocking action of 4-AP which in turn enhances calcium influx into the neuron thus prolonging nerve action potential and increasing transmitter release. Wesseling *et al.*, N. Eng. J. of Med. 310 (15), pp. 988-989 (Apr. 1984).

[0010] In the use of a drug for long-term therapy it is desirable that the drug be formulated so that it is suitable for once- or twice-daily administration to aid patient compliance. Further, in view of the nature of neurological diseases, it can be appreciated that there is a need for an improved dosage form. However, such a formulation must result in a controlled release of drug to the systemic circulation and therapeutically effective blood levels throughout a given treatment period.

[0011] Another problem with long-term therapy is the requirement of determining an optimum dose which can be tolerated by the patient. If such a dose is not determined this can lead to a diminution in the effectiveness of the drug being administered.

[0012] It is an object of the present invention to provide preparations suitable for the long-term administration of a mono- or di-aminopyridine active agent.

[0013] It is a further object of the present invention to provide the use of a mono- or di-aminopyridine active agent in a manner which enables one to achieve a tolerable state for said drug in a subject being treated therewith.

[0014] According to the invention there is provided a pharmaceutical formulation comprising a mono- or di-aminopyridine for oral administration on a once- or twice-daily basis, said formulation including said mono- or di-aminopyridine active agent in a polymer carrier effective to permit release of said mono- or di-aminopyridine at a rate allowing controlled absorption thereof over, on the average, not less than a 12 hour period and at a rate sufficient to achieve therapeutically effective blood levels over a period of 12-24 hours following oral administration, said rate being measured *in vitro* as a dissolution rate of said formulation, which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following:

a) no more than 50% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

b) no more than 75% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus; and

c) 100% of the mono- or di-aminopyridine is released no earlier than after 8 hours of measurement in said apparatus.

[0015] The pharmaceutical formulations according to the invention include pharmaceutical formulations for oral administration and pharmaceutical formulations for

administration by the percutaneous route.

[0016] According to one aspect of the invention there is provided a pharmaceutical formulation which comprises a pellet for oral administration, said pellet comprising a core of a mono- or di-aminopyridine or a pharmaceutically acceptable salt thereof in association with one or more pharmaceutically acceptable excipient(s), the mono- or di-aminopyridine component and the pharmaceutically acceptable excipient(s) being present in a ratio of from 10:1 to 1:20, and a multi-layer membrane surrounding said core and containing a major proportion of a pharmaceutically acceptable film-forming, water insoluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble polymer, the number of layers in said membrane and the ratio of said water soluble to water insoluble polymer, when said water soluble polymer is present, being effective to permit release of said mono- or di-aminopyridine from said pellet at a rate allowing controlled absorption thereof over, on the average, not less than a 12 hour period following oral administration, said rate being measured *in vitro* as a dissolution rate of said pellet, which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following:

a) no more than 50% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

b) no more than 75% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus; and

c) 100% of the mono- or di-aminopyridine is released no earlier than after 8 hours of measurement in said apparatus.

[0017] Thus the pharmaceutical formulations according to the invention for oral administration can be administered on a once- or twice-daily basis.

[0018] Preferred pharmaceutical formulations according to the invention for oral administration are in a multiparticulate form, from which the active agent is released at a rate to maintain therapeutically effective blood levels over a 12 hour period or a 24 hour period, as required.

[0019] According to one embodiment, the release of active agent from the pellet is at a rate allowing controlled absorption thereof over a 24 hour period following oral administration, said rate being measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. which substantially corresponds to the following dissolution pattern:

a) from 0 to 40% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

b) from 20 to 60% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 30 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus;

d) from 50 to 90% of the total mono- or di-aminopyridine is released after 12 hours of measurement in said apparatus; and

e) not less than 75% of the total mono- or di-aminopyridine is released after 24 hours of measurement in said apparatus.

[0020] The formulation for once-daily administration can include an amount of a rapid release form of the active agent as hereinafter described, so as to obtain a relatively immediate therapeutic response.

[0021] Pharmaceutical formulations according to the invention for once-daily administration can maintain therapeutically effective blood levels substantially over 24 hours with peak plasma levels occurring between 2 and 16 hours, more especially between 4 and 10 hours.

[0022] The desired time to peak plasma level is defined as the Tmax of the formulation.

[0023] According to a second embodiment, the release of active agent from the pellet is at a rate allowing controlled absorption thereof over a 12 hour period following oral administration, said rate being measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. which substantially corresponds to the following dissolution pattern:

a) from 0 to 40% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

b) from 20 to 60% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 30 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus; and

d) not less than 75% of the total is released after 12 hours of measurement in said apparatus.

[0024] The formulation for twice-daily administration can also include an amount of a rapid release form of the active agent as hereinafter described, so as to obtain a relatively intermediate therapeutic response.

[0025] Pharmaceutical formulations according to the

invention for twice-daily administration can maintain therapeutically effective blood levels substantially over 12 hours with peak plasma levels occurring between 1 and 10 hours, more especially between 2 and 8 hours.

[0026] The core of the pellet formulations according to the invention preferably comprises:

a) a powder mixture containing a mono- or di-aminopyridine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and

b) a polymeric material containing a major proportion of a pharmaceutically acceptable water soluble polymer and a minor proportion of a phatmaceutically acceptable water insoluble polymer,

said core comprising layers of said powder mixture and said polymeric material superimposed one upon the other and said polymeric material being present in an amount effective to ensure that all of said powder mixture is coated into said core.

[0027] The term water soluble polymer as used herein includes polymers which are freely permeable to water, whilst the term water insoluble polymer as used herein includes polymers which are slightly permeable to water, as hereinafter indicated.

[0028] Preferably the water soluble polymer in the core or membrane is the same or different and is selected from polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, agar, carrageenan, xanthan or polyethylene glycol or a mixture thereof.

[0029] Alternatively, the water soluble polymer in the core or membrane can be replaced by a polymeric material which is freely permeable to mono- or di-aminopyridine and water and comprises a copolymer of acrylic and methacrylic acid esters.

[0030] A suitable polymer which is freely permeable to mono- or di-aminopyridine and water is a polymer sold under the Trade Mark EUDRAGIT RL.

[0031] Preferably, the water insoluble polymer in the core or membrane is selected from ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene oxide), poly(ethylene terephtalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride) or polyurethane or a mixture thereof.

[0032] The water insoluble polymer of the core or membrane may also comprise naturally occuring polymers or resins.

[0033] Thus other preferred water insoluble polymers are selected from a naturally occuring polymer selected from shellac, chitosan, gum juniper or a mixture thereof.

[0034] Alternatively, the water insoluble polymer in the core or membrane can be replaced by a polymeric material which is slightly permeable to mono- or di-aminopyridine and water and comprises a copolymer of acrylic and methacrylic acid esters.

[0035] A suitable polymer which is slightly permeable to mono- or di-aminopyridine and water is a polymer sold under the Trade Mark EUDRAGIT RS or a polymer whose permeability is pH dependent and sold under the Trade Mark EUDRAGIT L, EUDRAGIT S or EUDRAGIT E. Especially preferred polymers in this category are EUDRAGIT S.

[0036] EUDRAGIT polymers are polymeric lacquer substances based on acrylates and/or methacrylates. The polymeric materials sold under the Trade Mark EUDRAGIT RL and EUDRAGIT RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups and are described in the "EUDRAGIT" brochure of Messrs. Rohm Pharma GmbH (1984) wherein detailed physical-chemical data of these products is given. The ammonium groups are present as salts and give rise to the permeability of the lacquer films. EUDRAGIT RL and RS are freely permeable (RL) or slightly permeable (RS), respectively, independent of pH.

[0037] EUDRAGIT S is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water. It becomes soluble in a neutral to weakly alkaline milieu by forming salts with alkalis. The permeability of EUDRAGIT S is pH dependent. Above pH 6.0 the polymer becomes increasingly permeable. EUDRAGIT S is described in the "EUDRAGIT S " brochure of Messrs. Rohm Pharma GmbH (1986) wherein detailed physical-chemical data of the product is given.

[0038] The core suitably has a number of layers of the core-forming materials and is built up in a manner known *per se*.

[0039] The active agent, pharmaceutically acceptable excipient(s) and the polymeric material can be built up on an inert core. The inert core is preferably a non-pareil seed of sugar/starch having an average diameter in the range 0.2 - 1.4 mm, more especially, 0.3 - 0.8 mm.

[0040] The mono- or di-aminopyridine and pharmaceutically acceptable excipient(s) are blended to form a homogeneous powder. The mono- or di-aminopyridine component and pharmaceutically acceptable excipient(s) are preferably present in a ratio of from 4:1 to 1:5, more especially 1:3 to 1:1.

[0041] The blend is suitably passed through an appropriate mesh screen using a milling machine. In the case of coating in a conventional coating pan, alternate lay-

ers of a coating solution/suspension of the polymeric material and the powder are applied to the central inert core to build up the multi-layer arrangement of the core. In the case of an automatic coating system, the coating solution/suspension of the polymeric material and the powder are applied, simultaneously, in conventional manner.

[0042] The coating solution/suspension of the polymeric material comprises one or more polymer(s) dissolved/suspended in a suitable solvent or mixture of solvents. The concentration of the polymeric material in the coating solution/suspension is determined by the viscosity of the final solution/suspension. Preferably, between 5 and 50 parts of the central inert cores are used relative to the homogeneous powder. The addition of a plasticizing agent to the polymeric solution/suspension may be necessary depending on the formulation to improve the elasticity and also the stability of the polymer film and to prevent changes in the polymer permeability over prolonged storage.

[0043] Such changes could affect the drug release rate. Suitable plasticizing agents include polyethylene glycol, propylene glycol, glycerol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, castor oil and varying percentages of acetylated monoglycerides.

[0044] Alternatively, the active agent, pharmaceutically acceptable excipient(s) and polymeric material can be built up on a central active core. The active core is suitably formed by blending the mono- or di-aminopyridine, pharmaceutically acceptable excipient(s) and polymeric material to form a homogeneous powder, shaping a portion of said blend to form a central core and applying the remainder of said blend alternately or simultaneously with a polymer binding solution to form a layered structure on said central core.

[0045] The completed active cores preferably have an average diameter in the range 0.4 - 1.6 mm, more especially, 0.6 - 1.2 mm.

[0046] The active core is formed by blending mono- or di-aminopyridine, pharmaceutically acceptable excipient(s) and polymeric material to form a homogeneous powder. A portion of the blend is shaped to form a central core. A multi-layer arrangement is then built up by a successive layering and binding process wherein the remainder of the blend and a polymer binding solution are applied to the active core in alternate layers in a conventional coating pan. Alternatively, an automatic coating system may be used wherein the remainder of the blend and polymer binding solution is applied to the active core, simultaneously. Conventional automated coating systems include for example a CF granulator or a Glatt fluidized bed. The cores are formed to assure a uniform distribution of mono- or di-aminopyridine and excipient ingredients throughout the cores.

[0047] As indicated above, the pellet formulations for oral administration in accordance with the invention can include an amount of a rapid release form of active agent so as to obtain a relatively immediate therapeutic response, together with the prolonged effects hereinabove described.

[0048] Thus according to a third embodiment of the invention there is provided a controlled absorption mono- or di-aminopyridine formulation for oral administation, comprising pellets as hereinbefore defined and including a sufficient quantity of a rapid release form of mono- or di-aminopyridine to ensure prompt achievement of therapeutically effective blood levels together with therapeutically effective blood levels over a 12 to 24 hour period following each oral administration.

[0049] A preferred such controlled absorption formulation in accordance with the invention has a dissolution rate which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following dissolution pattern:

a) from 20 to 60% of the total mono- or di-aminopyridine is released after 2 hours of measurement in said apparatus;

b) from 30 to 70% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 50 to 90% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus; and

d) not less than 75% of the total mono- or di-aminopyridine is released after 12 hours of measurement in said apparatus.

[0050] A preferred controlled absorption formulation in accordance with the invention for once-daily administration has a dissolution rate which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water and at 50 r.p.m. substantially corresponds to the following dissolution pattern:

a) from 10 to 40% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

b) from 25 to 65% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 40 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus;

d) from 50 to 90% of the total mono- or di-aminopyridine is released after 12 hours of measurement in said apparatus; and

e) not less than 75% of the total mono- or di-aminopyridine is released after 24 hours of measurement in said apparatus.

[0051] A preferred controlled absorption formulation in accordance with the invention for twice-daily administration has a dissolution rate which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water and at 50 r.p.m. substantially corresponds to the following dissolution pattern:

a) from 20 to 50% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

b) from 30 to 70% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 40 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus; and

d) not less than 75% of the total mono- or di-aminopyridine is released after 12 hours in said apparatus.

[0052] The controlled absorption formulation according to the invention can comprise a blend of pellets as hereinbefore defined, together with up to 60% by weight of said rapid release form of mono- or di-aminopyridine, more especially 10-40% by weight in the case of a once-daily formulation and 20-50% by weight in the case of a twice-daily formulation

[0053] The rapid release form of the active agent can comprise rapid release pellets or granulates.

[0054] Preferably, the rapid release pellets comprise a core of mono- or di-aminopyridine active agent or a pharmaceutically acceptable salt thereof in association with one or more pharmaceutically acceptable excipient(s), the mono- or di-aminopyridine component and the pharmaceutically acceptable excipient(s) being present in a ratio of from 10:1 to 1:20 and a multi-layer membrane surrounding said core and containing a major proportion of a pharmaceutically acceptable film-forming, water soluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water insoluble polymer, the number of layers in said membrane and the ratio of said water soluble to water insoluble polymer being effective to allow relatively immediate release of the active agent from said pellet.

[0055] Further, preferably, the pellets have a dissolution rate, which when measured *in vitro* in a type II dissolution apparatus according to US Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following dissolution pattern:

(a) not less than 70% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus; and

(b) not less than 85% of the total mono- or di-aminopyridine is released after 2 hours of measurement in said apparatus.

[0056] Depending on the function of the pellets, the polymeric material of the core or membrane will consist solely of a water insoluble polymer or a polymer which is slightly permeable to water and aqueous solutions of mono- or di-aminopyridine. However, the polymeric material of the core or membrane may also consist solely of a water soluble polymer or a polymer which is freely permeably to aqueous solutions of mono- or di-aminopyridine in water, especially in the case of the rapid release pellets.

[0057] The polymeric material of the core preferably consists solely of a water insoluble polymer or a polymer which is slightly permeable to water and aqueous solutions of mono- or di-aminopyridine. Alternatively, the polymeric material of the core may consist solely of a water soluble polymer or a polymer which is freely permeable to aqueous solutions of mono- or di-aminopyridine and water as indicated above. The polymeric material of the core may include a combination of a water insoluble polymer with a water soluble polymer. The ratio of water soluble/freely permeable to water insoluble/slightly permeable polymer is determined by the particular combination of polymers selected.

[0058] The term pharmaceutically acceptable excipient is used herein to define material(s) which is/are homogeneously mixed with the mono- or di-aminopyridine to form the pellet. These materials may also include ingredients known to act as lubricants. Representative excipients include: microcrystalline cellulose (such as that sold under the Trade Mark AVICEL); colloidal silicon dioxide (such as that sold under the Trade Mark AEROSIL); lactose; talc; starch; sorbitol; and cyclodextrin. These may be used singly or in combination with each other. Especially preferred excipients are talc and lactose.

[0059] Preferred coating materials include - solutions/suspensions of the polymers cited for use in the application of the powder blend to the central cores in a suitable organic/aqueous carrier medium.

[0060] The membrane of the film-forming polymer or mixture of polymers surrounding the core preferably has a proportion of a polymer which is slightly permeable to mono- or di-aminopyridine and water and optionally a proportion of a water permeable polymer, the ratio of water slightly permeable to water permeable polymer being determined by the inherent permeability characteristics of the polymer(s) selected.

[0061] As indicated above, the membrane may also be composed of a proportion of a polymer which is water insoluble and a proportion of a polymer which is

water soluble, the ratio of water insoluble to water soluble polymer being determined by the inherent permeability characteristics of the respective polymers.

[0062] Normally the ratio of water insoluble/slightly permeable polymers to water soluble/permeable polymers lies between 1:5 and 50:1, more especially 1:2 and 20:1. Examples of each of these types of polymer are described above. Especially suitable water soluble/permeable polymers include polyvinylpyrrolidone, polyvinyl alcohol and EUDRAGIT RL, whilst suitable water insoluble/slightly permeable polymers include ethyl cellulose, cellulose acetate, EUDRAGIT RS, EUDRAGIT L, EUDRAGIT E and EUDRAGIT S. Commercially available ready-made polymeric solutions/suspensions may also be used. These ready-made solutions/suspensions may optionally contain plasticizing agents to improve the polymer film as hereinbefore described. Examples of ready-made solutions/suspensions of polymeric material with or without plasticizing agent include EUDRAGIT RL 30D, EUDRAGIT NE 30D, EUDRAGIT E 12.5, EUDRAGIT L 12.5 P, EUDRAGIT E 12.5, EUDRAGIT S 12.5 P, EUDRAGIT RL 12.5, EUDRAGIT RS 300, EUDRAGIT RS 12.5, AQUACOAT (a Trade Mark of FMC Corporation) and SURE-LEASE (a Trade Mark of Colorcon Inc.).

[0063] The water insoluble polymer of the membrane may also comprise naturally occurring polymers or resins. Especially suitable water insoluble, naturally occuring polymers include shellac, chitosan, gum juniper or a mixture thereof.

[0064] The membrane may be built up by applying a plurality of coats of membrane polymer solution or suspension to the core as hereinafter described. The membrane solution or suspension contains the polymer(s) dissolved or suspended, respectively, in a suitable aqueous or organic solvent or mixture of solvents, optionally in the presence of a lubricant. Suitable lubricants are talc, stearic acid, magnesium stearate and sodium stearate. A particularly preferred lubricant is talc. The membrane, polymer or mixture of polymers may optionally include a plasticizing agent, the function and choice of which has been previously described.

[0065] The dissolution rate achieved is proportionally slower as the amount of membrane applied is increased.

[0066] The membrane solution or suspension may be applied to the active cores in a conventional coating pan as indicated or, alternatively, using an automated system such as a CF granulator, for example, a FREUND CF granulator, a GLATT fluidised bed processor, an AEROMATIC, a modified ACCELA-COTA or any other suitably automated bead coating equipment (FREUND, GLATT, AEROMATIC and ACCELA-COTA are all Trade Marks).

[0067] Preferably 2-75 ml of membrane solution/suspension is applied per application per kilogram of cores. In an automated system the total amount of membrane solution/suspension applied to the cores is the same as that applied in a conventional coating pan, except that the membrane solution/suspension may be applied continuously.

[0068] Preferably, when a coating pan is used the membrane is applied at a rate of 5-30 applications/day until all of the applications have been applied. Between days the pellets are dried for a suitable period of time at a controlled temperature.

[0069] The type II dissolution apparatus referred to above is a paddle-type apparatus for carrying out method II according to U.S. Pharmacopoeia XXII.

[0070] The pellets or granulates may be compressed into tablets using a binder and/or hardening agent commonly employed in tabletting such as microcrystalline cellulose sold under the Trade Mark "AVICEL" or a co-crystallised powder of highly modified dextrins (3% by weight) and sucrose sold under the Trade Mark "DI-PAC" in such a way that the specific dissolution rate of the pellets is maintained.

[0071] Pellets or a combination of pellets in accordance with the invention may also be filled into hard or soft gelatine capsules.

[0072] The mono- or di-aminopyridine active agent can form quaternary ammonium-type salts. However, given the solubility of mono- or di-aminopyridines, the formation of pharmaceutically acceptable salts would not normally be required.

[0073] The invention also provides use of a mono- or di-aminopyridine active agent for the manufacture of a medicament for use in the treatment of a neurological disease characterised by a slowing of nerve impulse transmission, wherein said medicament is effective to permit release of said active agent in a manner which achieves therapeutically effective blood levels over a 12-24 hour period when administered typically on a once- or twice-daily basis.

[0074] The mono- or di-aminopyridine active agent is particularly suitable for use in the treatment of a neurological disease which is characterised by demyelination of the central nervous system, more especially multiple sclerosis.

[0075] The mono- or di-aminopyridine active agent in accordance with the invention is also suitable for the treatment of Alzheimer's disease.

[0076] In one embodiment the medicament is administered to a subject at a dose and for a period sufficient to allow said subject to tolerate said dose without showing any adverse effects and thereafter increasing the dose of said active agent at selected intervals of time until a therapeutic dose is achieved.

[0077] In this embodiment of the invention at the commencement of treatment the active agent is preferably administered at a dose less than 15 mg/day until a tolerable state is reached. Suitably when said tolerable state is reached, the dose administered is increased by amounts of at least 5-15 mg/day until said therapeutic dose is reached.

[0078] The active agent is preferably 4-aminopyridine

or 3,4-di-aminopyridine.

[0079] The medicament is suitably formulated as a pharmaceutical formulation as hereinbefore specified.

[0080] In certain circumstances, the attending physician may consider it appropriate to administer the active agent both orally and percutaneously either simultaneously, separately or sequentially to achieve maximum therapeutic blood levels of said active agent.

[0081] The invention will be further illustrated by the following Examples.

Example 1

[0082] 4-AP (8.0 Kg), talc (12.0 Kg) and lactose (36.0 Kg) were blended and milled through a mill equipped with a 50 mesh screen so as to obtain a homogeneous powder. The powder was applied to starch/sugar seeds (0.4-5.0 mm) (12.0 Kg) using a Freund CF granulator and a coating solution of 3.5% polyvinylpyrrolidone in isopropanol to form the cores.

[0083] A membrane was then applied to the cores by spraying on a solution consisting of:

12.5% EUDRAGIT S in acetone/isopropanol 40:60
100 parts by weight

Isopropanol
100 parts by weight

while at the same time but separately dusting on talc (100 parts by weight) in conventional manner. The ratio of membrane solution to talc applied was 0.62 g of talc per gram of membrane solution. A sufficient amount of membrane solution and talc was applied to 68.0 Kg of cores to achieve the dissolution profile given below.

[0084] The finished pellets were dried to evaporate all solvents prior to performing the dissolution profile.

[0085] The dissolution rate of the pellets was tested by method II for the U.S. Pharmacopoeia XXII in water at 50 r.p.m. The dissolution rate was as follows:

Time	% Release
1	0.4
4	34.9
8	68.7
12	85.4
24	99.4

[0086] The coated beads were blended with active (rapid release) beads in a ratio of 15:85 of active:coated beads by content of 4-AP to generate the following *in vitro* dissolution profile:

Time	% Release
1	14.9
4	42.7
8	73.6
12	89.3
24	100.2

Example 2

[0087] 4-AP (4.0 Kg), talc (6.0 Kg) and lactose (18.0 Kg) were blended and milled through a mill equipped with a 50 mesh screen so as to obtain a homogeneous powder. This powder blend was layered into spherical cores using a Freund CF granulator and a coating solution of 3.5% polyvinylpyrrolidone in isopropanol.

[0088] A membrane was then applied to the cores by spraying on a solution consisting of:

12.5% EUDRAGIT RS in acetone/ isopropanol 40:60
50 parts by weight

12.5% EUDRAGIT S in acetone/isopropanol 40:60
50 parts by weight

Isopropanol
100 parts by weight

while at the same time but separately dusting on talc (100 parts by weight) in conventional manner. The ratio of membrane solution to talc applied was 0.62 g of talc per gram of membrane solution. A sufficient amount of membrane solution and talc was applied to 28.0 Kg of cores to achieve the dissolution profile given below.

[0089] The finished pellets were dried to evaporate all solvents prior to performing the dissolution profile.

[0090] The dissolution rate of the pellets was tested by method II for the U.S. Pharmacopoeia in water at 50 r.p.m. The dissolution rate was as follows:

Time	% Release
1	1.6
4	25.5
8	58.5
12	79.6
24	97.0

[0091] On blending with 20% of active beads based

on total content of 4-AP the following dissolution profile resulted:

Time	% Release
1	19.7
4	40.9
8	64.9
12	81.2
24	96.8

Example 3

[0092] The procedure used was the same as that outlined in Example 2 with the exception that the active beads were formed in a Glatt fluidised coating apparatus.

[0093] The active pellets were coated on the Glatt apparatus with a mixture of polymers comprising EUDRAGIT RS:EUDRAGIT S in the ratio 1:2 to achieve the following release profile:

Time	% Release
1	2.5
4	29.9
8	69.5
12	96.2

[0094] These pellets were combined with rapid release pellets in a ratio of 30:70 to generate the following release rates:

Time	% Release
1	30.9
4	49.7
8	77.6
12	97.4

Example 4

[0095] The active pellets from Example 3 were coated in a Glatt fluidised bed apparatus using a dispersion of EUDRAGIT polymers in water and containing talc and triacetin. The EUDRAGIT polymers consisted of a ratio of 19:1 of EUDRAGIT RS 30D to EUDRAGIT RL 30D by weight of polymer and the total solid content of the polymer dispersion, including the lubricant (talc) and plasticizer (triacetin) was 23.5%. Following coating and drying, the dissolution rate of the beads according to type II USP apparatus was as follows:

Time	% Release
1	4.6
4	39.5
8	61.2
12	76.6
24	86.2

[0096] When blended with active beads in a ratio of 25:75 of active:coated beads by total content of 4-AP the following dissolution profile in the same apparatus was achieved:

Time	% Release
1	28.6
4	54.6
8	70.9
12	82.5
24	91.4

Example 5

[0097] Active 4-AP beads/pellets were formulated according to the procedure set out in Example 1. These active pellets were coated according to the procedure set out in Example 2, however, the application of coats was such as to provide a form of 4-AP suitable for twice daily administration. The dissolution profile of the coated beads was as follows:

Time	% Release
1	23.6
4	45.2
8	76.4
12	96.2

Example 6

[0098] Pellets obtained in Example 2 were further coated to the following dissolution rate:

Time	% Release
1	1.9
4	21.3
8	53.7
12	83.4

[0099] On blending with active 4-AP beads in a ratio of 30:70 of active:coated by content of 4-AP, the following dissolution profile resulted:

Time	% Release
1	31.6
4	44.2
8	66.8
12	89.1

Example 7

[0100] 4-AP (12.0 Kg), talc (8.0 Kg) and lactose (24.0 Kg) were blended and milled through a mill equipped with a 50 mesh screen so as to obtain a homogeneous powder. The powder was applied to starch/sugar seeds (0.5-0.6 mm) (16.0 Kg) using a Freund CF granulator and a coating solution of 3.5% polyvinylpyrrolidone in isopropanol to form the cores.

[0101] A membrane was then applied to the cores by spraying on a solution consisting of:

12.5% EUDRAGIT RS in acetone/isopropanol 40:60
100 parts by weight

Isopropanol
50 parts by weight

while at the same time but separately dusting on talc (50 parts by weight) in conventional manner. The ratio of membrane solution to talc applied was 0.41 g of talc per gram of membrane solution. A sufficient amount of membrane solution and talc was applied to 60.0 Kg of cores to achieve the dissolution profile given below.

[0102] The finished pellets were dried to evaporate all solvents prior to performing the dissolution profile.

[0103] The dissolution rate of the pellets was tested by method II for the U.S. Pharmacopoeia XXII in water at 50 r.p.m. The dissolution rate was as follows:

Time	% Release
1	1.6
4	29.8
8	59.4
12	77.7
24	92.8

[0104] The coated beads were blended with active (rapid release) beads in a ratio of 20:80 of active:coated beads by content of 4-AP to generate the following *in vitro* dissolution profile:

Time	% Release
1	21.3
4	43.9
8	66.5
12	82.4
24	93.7

Example 8

[0105] 3,4-DAP (8.0 Kg), talc (12.0 Kg) and lactose (36.0 Kg) were blended and milled through a mill equipped with a 50 mesh screen so as to obtain a homogeneous powder. This powder blend was layered into spherical cores using a Freund CF granulator and a coating solution of 3.5% polyvinylpyrrolidone in isopropanol.

[0106] A membrane was then applied to the cores by spraying on a solution consisting of:

12.5% EUDRAGIT RS in acetone/isopropanol 40:60
50 parts by weight

12.5% EUDRAGIT S in acetone/isopropanol 40:60
50 parts by weight

Isopropanol
100 parts by weight

while at the same time but separately dusting on talc (100 parts by weight) in conventional manner. The ratio of membrane solution to talc applied was 0.62 g of talc per gram of membrane solution. A sufficient amount of membrane solution and talc was applied to 56.0 Kg of

cores to achieve the dissolution profile given below.

[0107] The finished pellets were dried to evaporate all solvents prior to performing the dissolution profile.

[0108] The dissolution rate of the pellets was tested by method II for the U.S. Pharmacopoeia XXII in water at 50 r.p.m. The dissolution rate was as follows:

Time	% Release
1	3.7
4	29.6
8	51.4
12	72.6
24	98.4

[0109] On blending with 25% of active beads based on total content of 3,4-DAP the following dissolution profile resulted:

Time	% Release
1	28.2
4	44.3
8	64.2
12	77.1
24	99.3

Example 9

[0110] The procedure used was the same as that outlined in Example 2 with the exception that the active beads were formed in a Glatt fluidised coating apparatus.

[0111] The active beads were coated on the Glatt apparatus with a mixture of polymers comprising EUDRAGIT RS:EUDRAGIT S in the ratio 1:2 to achieve the following release profile:

Time	% Release
1	3.6
4	28.6
8	60.9
12	88.8

[0112] These pellets were combined with rapid release pellets in a ratio of 30:70 to generate the following release rates:

Time	% Release
1	29.7
4	50.1
8	69.3
12	90.4

Example 10

[0113] The active beads from Example 3 were coated in a Glatt fluidised bed apparatus using a dispersion of EUDRAGIT polymers in water and containing talc and triacetin. The EUDRAGIT polymers consisted of a ratio of 9:1 of EUDRAGIT RS 30D to EUDRAGIT RL 30D by weight of polymer and the total solid content of the polymer dispersion, including the lubricant (talc) and plasticizer (triacetin) was 18.5%. Following coating and drying, the dissolution rate of the beads according to type II USP apparatus was as follows:

Time	% Release
1	7.6
4	41.4
8	65.2
12	77.4
24	92.6

[0114] When blended with active beads in a ratio of 15.8 of active:coated beads by total content of 4-AP the following dissolution profile in the same apparatus was achieved:

Time	% Release
1	22.5
4	50.7
8	72.6
12	79.3
24	93.7

Claims

1. A pharmaceutical formulation comprising a mono- or di-aminopyridine for oral administration on a once- or twice-daily basis, said formulation including said mono- or di-aminopyridine active agent in a polymer carrier effective to permit release of said mono- or di-aminopyridine at a rate allowing controlled absorption thereof over, on the average, not less than a 12 hour period and at a rate sufficient to achieve therapeutically effective blood levels over a period of 12-24 hours following oral administration, said rate being measured *in vitro* as a dissolution rate of said formulation, which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following:

   a) no more than 50% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

   b) no more than 75% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus; and

   c) 100% of the mono- or di-aminopyridine is released no earlier than after 8 hours of measurement in said apparatus.

2. A pharmaceutical formulation according to Claim 1, which comprises a pellet for oral administration, said pellet comprising a core of a mono- or di-aminopyridine or a pharmaceutically acceptable salt thereof in association with one or more pharmaceutically acceptable excipient(s), the mono- or di-aminopyridine component and the pharmaceutically acceptable excipient(s) being present in a ratio of from 10:1 to 1:20, and a multi-layer membrane surrounding said core and containing a major proportion of a pharmaceutically acceptable film-forming, water insoluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble polymer, the number of layers in said membrane and the ratio of said water soluble to water insoluble polymer, when said water soluble polymer is present, being effective to permit release of said mono- or di-aminopyridine from said pellet at a rate allowing controlled absorption thereof over, on the average, not less than a 12 hour period following oral administration, said rate being measured *in vitro* as a dissolution rate of said pellet, which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following:

   a) no more than 50% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

   b) no more than 75% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus; and

   c) 100% of the mono- or di-aminopyridine is released no earlier than after 8 hours of measurement in said apparatus.

3. A pharmaceutical formulation according to Claim 2, wherein the release of mono- or di-aminopyridine from said pellet is at a rate allowing controlled absorption thereof over a 24 hour period following oral administration, said rate being measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. which substantially corresponds to the following dissolution pattern:

   a) from 0 to 40% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

   b) from 20 to 60% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

   c) from 30 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus;

   d) from 50 to 90% of the total mono- or di-aminopyridine is released after 12 hours of measurement in said apparatus; and

   e) not less than 75% of the total mono- or di-aminopyridine is released after 24 hours of measurement in said apparatus.

4. A pharmaceutical formulation according to Claim 2, wherein the release of mono- or di-aminopyridine from said pellet is at a rate allowing controlled absorption thereof over a 12 hour period following oral administration, said rate being measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. which substantially corresponds to the following dissolution pattern:

   a) from 0 to 40% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

   b) from 20 to 60% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 30 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus; and

d) not less than 75% of the total is released after 12 hours of measurement in said apparatus.

5. A pharmaceutical formulation according to any one of Claims 2 to 4, wherein the core comprises:

a) a powder mixture containing a mono- or di-aminopyridine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and

b) a polymeric material containing a major proportion of a pharmaceutically acceptable water soluble polymer and a minor proportion of a pharmaceutically acceptable water insoluble polymer,

said core comprising layers of said powder mixture and said polymeric material superimposed one upon the other and said polymeric material being present in an amount effective to ensure that all of said powder mixture is coated into said core.

6. A pharmaceutical formulation according to any one of Claims 2 to 5, wherein the water soluble polymer in the core or membrane is the same or different and is selected from polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, agar, carrageenan, xanthan or polyethylene glycol or a mixture thereof.

7. A pharmaceutical formulation according to any one of Claims 2 to 5, wherein the water soluble polymer in the core or membrane is replaced by a polymeric material which is freely permeable to mono- or di-aminopyridine and water and comprises a copolymer of acrylic and methacrylic acid esters.

8. A pharmaceutical formulation according to any one of Claims 2 to 7, wherein the water insoluble polymer in the core or membrane is selected from ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene oxide), poly(ethylene terephtalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride), polyurethane or a mixture thereof or a naturally occurring polymer selected from shellac, chitosan, gum juniper or a mixture thereof.

9. A pharmaceutical formulation according to any one of Claims 2 to 8, wherein the water insoluble polymer in the core or membrane is replaced by a polymeric material which is slightly permeable to mono- or di-aminopyridine and water and comprises a copolymer of acrylic and methacrylic acid esters.

10. A process for the production of a pharmaceutical formulation according to any one of Claims 2 to 9, which comprises forming a core of mono- or di-aminopyridine or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable excipient(s) and enclosing the core in a membrane of a film-forming polymer or mixture thereof as defined in Claim 2 which permits release of the mono- or di-aminopyridine or the pharmaceutically acceptable salt thereof in the manner set out in any one of Claims 2 to 4.

11. A pharmaceutical formulation comprising pellets according to any one of Claims 2 to 9, said formulation including a sufficient quantity of a rapid release form of mono- or di-aminopyridine to ensure prompt achievement of therapeutically effective blood levels together with therapeutically effective blood levels over a 12 to 24 hour period following each oral administration.

12. A pharmaceutical formulation according to Claim 11, which has a dissolution rate which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following dissolution pattern:

a) from 20 to 60% of the total mono- or di-aminopyridine is released after 2 hours of measurement in said apparatus;

b) from 30 to 70% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 50 to 90% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus; and

d) not less than 75% of the total mono- or di-aminopyridine is released after 12 hours of measurement in said apparatus.

13. A pharmaceutical formulation according to Claim 11, which has a dissolution rate which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water and at 50 r.p.m. substantially corresponds to the following dissolution pattern:

a) from 10 to 40% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

b) from 25 to 65% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 40 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus;

d) from 50 to 90% of the total mono- or di-aminopyridine is released after 12 hours of measurement in said apparatus; and

e) not less than 75% of the total mono- or di-aminopyridine is released after 24 hours of measurement in said apparatus.

14. A pharmaceutical formulation according to Claim 11, which has a dissolution rate which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water and at 50 r.p.m. substantially corresponds to the following dissolution pattern:

a) from 20 to 50% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

b) from 30 to 70% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 40 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus; and

d) not less than 75% of the total mono- or di-aminopyridine is released after 12 hours in said apparatus.

15. A pharmaceutical formulation according to any one of Claims 11 to 14, which comprises a blend of pellets according to any one of Claims 2 to 9, together with up to 60% by weight of said rapid release form of mono- or di-aminopyridine, especially rapid release pellets.

16. A pharmaceutical formulation according to Claim 15, wherein the rapid release pellets comprise a core of mono- or di-aminopyridine active agent or a pharmaceutically acceptable salt thereof in association with one or more pharmaceutically acceptable excipient(s), the mono- or di-aminopyridine component and the pharmaceutically acceptable excipient(s) being present in a ratio of from 10:1 to 1:20 and a multi-layer membrane surrounding said core and containing a major proportion of a pharmaceutically acceptable film-forming, water soluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water insoluble polymer, the number of layers in said membrane and the ratio of said water soluble to water insoluble polymer being effective to allow relatively immediate release of the active agent from said pellet.

17. A pharmaceutical formulation according to Claim 16, wherein the pellets have a dissolution rate, which when measured *in vitro* in a type II dissolution apparatus according to US Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following dissolution pattern:

(a) not less than 70% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus; and

(b) not less than 85% of the total mono- or di-aminopyridine is released after 2 hours of measurement in said apparatus.

18. A pharmaceutical formulation according to any one of Claims 1-9 or 11-17, from which the mono- or di-aminopyridine active agent is released at a rate allowing controlled absorption thereof over a twenty-four hour period following oral administration, said rate being measured *in vivo* and having a Tmax between 2 and 16 hours and achieving minimum effective blood levels from 12 to 20 hours over a 24 hour period.

19. Use of a mono- or di-aminopyridine active agent for the manufacture of a medicament for use in the treatment of a neurological disease characterised by a slowing of nerve impulse transmission, wherein said medicament is effective to permit release of said active agent in a manner which achieves therapeutically effective blood levels over a 12-24 hour period when administered on a once- or twice-daily basis.

20. Use according to Claim 19, wherein the neurological disease is characterised by demyelination of the central nervous system, in particular multiple sclerosis.

21. Use according to Claim 19, wherein the neurological disease is Alzheimer's disease.

22. Use according to any one of Claims 19-21, wherein said medicament is administered to a subject at a dose and for a period sufficient to allow said subject to tolerate said dose without showing any adverse effects and thereafter increasing the dose of said active agent at selected intervals of time until a therapeutic dose is achieved.

23. Use according to Claim 22, wherein at the commencement of treatment the active agent is administered at a dose of less than 15 mg/day until a tolerable state is reached.

24. Use according to Claim 23, wherein when said tolerable state is reached, the dose administered is increased by amounts of at least 5-15 mg/day until said therapeutic dose is reached.

Patentansprüche

1. Pharmazeutische Formulierung, enthaltend ein Mono- oder Diaminopyridin zur oralen Verabreichung auf einer einmal oder zweimal täglichen Basis, wobei die Formulierung den Mono- oder Diaminopyridin-Wirkstoff in einem polymeren Trägerstoff enthält, der wirksam ist, um das Mono- oder Diaminopyridin mit einer Geschwindigkeit freizusetzen, die dessen kontrollierte Absorption während eines Zeitraums von durchschnittlich nicht weniger als 12 h und mit einer Geschwindigkeit, die ausreicht, um therapeutisch wirksame Blutkonzentrationen während eines Zeitraum von 12-24 h nach der oralen Verabreichung zu erzielen, gestattet, wobei die Geschwindigkeit *in vitro* als Auflösungsgeschwindigkeit der Formulierung gemessen wird, die beim Messen in einem Löseapparat vom Typ II nach der U.S.-Pharmacopoeia XXII in Wasser bei 50 U/min im wesentlichen folgendem entspricht:

   a) nicht mehr als 50 % des gesamten Mono- oder Diaminopyridins werden nach 1 h Meßzeit in dem Gerät freigesetzt;

   b) nicht mehr als 75 % des gesamten Mono- oder Diaminopyridins werden nach 4 h Meßzeit in dem Gerät freigesetzt; und

   c) 100 % des Mono- oder Diaminopyridins werden erst nach 8 h Meßzeit in dem Gerät freigesetzt.

2. Pharmazeutische Formulierung nach Anspruch 1, die ein Pellet zur oralen Verabreichung enthält, wobei das Pellet folgendes enthält: einen Kern aus einem Mono- oder Diaminopyridin oder aus einem pharmazeutisch verträglichen Salz hiervon in Verbindung mit einem oder mehreren pharmazeutisch verträglichen Hilfsstoff(en), wobei die Mono- oder Diaminopyridin-Komponente und der(die) pharmazeutisch verträgliche(n) Hilfsstoff(e) in einem Verhältnis von 10:1 bis 1:20 vorhanden sind, und eine Mehrschichtenmembran, die den Kern umgibt und als Hauptteil ein pharmazeutisch verträgliches filmbildendes, wasserunlösliches Polymeres und gegebenenfalls einen kleineren Teil eines pharmazeutisch verträglichen, filmbildenden, wasserlöslichen Polymeren enthält, wobei die Anzahl der Schichten in der Membran und das Verhältnis von wasserlöslichem zu wasserunlöslichem Polymeren, wenn das wasserlösliche Polymere vorhanden ist, wirksam ist, um das Mono- oder Diaminopyridin aus dem Pellet mit einer Geschwindigkeit freizusetzen, die die kontrollierte Absorption davon während eines Zeitraums von durchschnittlich nicht weniger als 12 h nach der oralen Verabreichung gestattet, wobei die Geschwindigkeit *in vitro* als Auflösungsgeschwindigkeit des Pellets gemessen wird, die beim Messen in einem Löseapparat vom Typ II nach der U.S.-Pharmacopoeia XXII in Wasser bei 50 U/min im wesentlichen folgendem entspricht:

   a) nicht mehr als 50 % des gesamten Mono- oder Diaminopyridins werden nach 1 h Meßzeit in dem Gerät freigesetzt;

   b) nicht mehr als 75 % des gesamten Mono- oder Diaminopyridins werden nach 4 h Meßzeit in dem Gerät freigesetzt; und

   c) 100 % des Mono- oder Diaminopyridins werden erst nach 8 h Meßzeit in dem Gerät freigesetzt.

3. Pharmazeutische Formulierung nach Anspruch 2, wobei die Freisetzung des Mono- oder Diaminopyridins aus dem Pellet mit einer Geschwindigkeit erfolgt, die die kontrollierte Absorption davon während eines Zeitraums von 24 h nach der oralen Verabreichung gestattet, wobei die Geschwindigkeit in einem Löseapparat vom Typ II nach der U.S.-Pharmacopoeia XXII in Wasser bei 50 U/min gemessen ist, was im wesentlichen dem folgenden Auflösungsmuster entspricht:

   a) 0 bis 40 % des gesamten Mono- oder Diaminopyridins werden nach einer Meßzeit von 1 h in dem Gerät freigesetzt;

   b) 20 bis 60 % des gesamten Mono- oder Diaminopyridins werden nach einer Meßzeit von 4 h in dem Gerät freigesetzt;

c) 30 bis 80 % des gesamten Mono- oder Diaminopyridins werden nach einer Meßzeit von 8 h in dem Gerät freigesetzt;

d) 50 bis 90 % des gesamten Mono- oder Diaminopyridins werden nach einer Meßzeit von 12 h in dem Gerät freigesetzt; und

e) nicht weniger als 75 % des gesamten Mono- oder Diaminopyridins werden nach einer Meßzeit von 24 h in dem Gerät freigesetzt.

4. Pharmazeutische Formulierung nach Anspruch 2, wobei die Freisetzung des Mono- oder Diaminopyridins aus dem Pellet mit einer Geschwindigkeit erfolgt, die die kontrollierte Absorption davon während eines Zeitraums von 12 h nach der oralen Verabreichung gestattet, wobei die Geschwindigkeit in einem Löseapparat vom Typ II nach der U.S.-Pharmacopoeia XXII in Wasser bei 50 U/min gemessen ist, was im wesentlichen dem folgenden Auflösungsmuster entspricht:

a) 0 bis 40 % des gesamten Mono- oder Diaminopyridins werden nach einer Meßzeit von 1 h in dem Gerät freigesetzt;

b) 20 bis 60 % des gesamten Mono- oder Diaminopyridins werden nach einer Meßzeit von 4 h in dem Gerät freigesetzt;

c) 30 bis 80 % des gesamten Mono- oder Diaminopyridins werden nach einer Meßzeit von 8 h in dem Gerät freigesetzt; und

d) nicht weniger als 75 % des gesamten Mono- oder Diaminopyridins werden nach einer Meßzeit von 12 h in dem Gerät freigesetzt.

5. Pharmazeutische Formulierung nach einem der Ansprüche 2 bis 4, wobei der Kern folgendes enthält:

a) ein Pulvergemisch, das ein Mono- oder Diaminopyridin oder ein pharmazeutisch verträgliches Salz hiervon und einen pharmazeutisch verträglichen Hilfsstoff enthält, und

b) ein Polymermaterial, das als Hauptteil ein pharmazeutisch verträgliches, wasserlösliches Polymeres und einen kleineren Teils eines pharmazeutisch verträglichen, wasserunlöslichen Polymeren enthält,

wobei der Kern Schichten des Pulvergemisches und des Polymermaterials jeweils übereinander geschichtet enthält und das Polymermaterial in einer Menge vorhanden ist, die dazu wirksam ist, das Schichten des gesamten Pulvergemisches zu dem Kern zu gewährleisten.

6. Pharmazeutische Formulierung nach einem der Ansprüche 2 bis 5, wobei das wasserlösliche Polymere im Kern oder in der Membran gleich oder verschieden ist und ausgewählt ist aus Polyvinylalkohol, Polyvinylpyrrolidon, Methylcellulose, Hydroxpropylcellulose, Hydroypropylmethylcellulose, Agar, Carrageenan, Xanthan oder Polyethylenglycol oder einem Gemisch hiervon.

7. Pharmazeutische Formulierung nach einem der Ansprüche 2 bis 5, wobei das wasserlösliche Polymere in dem Kern oder in der Membran durch ein polymeres Material ersetzt ist, das für Mono- oder Diaminopyridin und Wasser frei durchlässig ist und ein Copolymeres von Acrylsäure- und Methacrylsäureestern enthält.

8. Pharmazeutische Formulierung nach einem der Ansprüche 2 bis 7, wobei das wasserunlösliche Polymere im Kern oder in der Membran ausgewählt ist aus Ethylcellulose, Celluloseacetat, Cellulosepropionat (niedriges, mittleres oder hohes Molekulargewicht), Celluloseacetatpropionat, Celluloseacetatbutyrat, Celluloseacetatphthalat, Cellulosetriacetat, Poly(methylmethacrylat), Poly(ethylmethacrylat), Poly(butylmethacrylat), Poly(isobutylmethacrylat), Poly(hexylmethacrylat), Poly(isodecylmethacrylat), Poly(laurylmethacrylat), Poly(phenylmethacrylat), Poly(methylacrylat), Poly(isopropylacrylat), Poly(isobutylacrylat), Poly(ocatdecylacrylat), Poly(ethylen), Poly(ethylen) mit niedriger Dichte, Poly(ethylen) mit hoher Dichte, Poly(propylen), Poly(ethylenoxid), Poly(ethylenterephthalat), Poly(vinylisobutylether), Poly(vinylacetat), Poly(vinylchlorid), Polyurethan oder aus einem Gemisch hiervon oder aus einem natürlich vorkommenden Polymeren, ausgewählt aus Schellack, Chitosan, Wacholderharz oder einem Gemisch hiervon.

9. Pharmazeutische Formulierung nach einem der Ansprüche 2 bis 8, wobei das wasserunlösliche Polymere im Kern oder in der Membran durch ein polymeres Material ersetzt ist, das für Mono- oder Diaminopyridin und Wasser etwas durchlässig ist und ein Copolymeres von Acrylsäure- und Methacrylsäureestern enthält.

10. Verfahren zur Herstellung einer pharmazeutischen Formulierung nach einem der Ansprüche 2 bis 9, das folgendes umfaßt: Bilden eines Kerns aus Mono- oder Diaminopyridin oder einem pharmazeutisch verträglichen Salz hiervon und aus (einem) pharmazeutisch verträglichen Hilfsstoff(en) und Umhüllen des Kerns mit einer Membran aus

einem filmbildenden Polymeren oder aus einem Gemisch von Polymeren nach Anspruch 2, die die Freisetzung des Mono- oder Diaminopyridins oder des pharmazeutisch verträglichen Salzes hiervon auf eine nach einem der Ansprüche 2 bis 4 definierte Weise gestatten.

11. Pharmazeutische Formulierung, die Pellets nach einem der Ansprüche 2 bis 9 enthält, wobei die Formulierung eine ausreichende Menge einer schnell freisetzenden Form von Mono- oder Diaminopyridin enthält, um das prompte Erreichen von therapeutisch wirksamen Blutkonzentrationen in Verbindung mit therapeutisch wirksamen Blutspiegeln während eines Zeitraums von 12 bis 24 h, jeweils nach der oralen Verabreichung, zu gewährleisten.

12. Pharmazeutische Formulierung nach Anspruch 11, die eine Auflösungsgeschwindigkeit aufweist, die beim Messen in einem Löseapparat vom Typ II nach der U.S.-Pharmacopoeia XXII in Wasser bei 50 U/min im wesentlichen dem folgenden Auflösungsmuster entspricht:

a) 20 bis 60 % des gesamten Mono- oder Diaminopyridins werden nach 2 h Meßzeit in dem Gerät freigesetzt;

b) 30 bis 70 % des gesamten Mono- oder Diaminopyridins werden nach 4 h Meßzeit in dem Gerät freigesetzt;

c) 50 bis 90 % des gesamten Mono- oder Diaminopyridins werden nach 8 h Meßzeit in dem Gerät freigesetzt; und

d) nicht weniger als 75 % des gesamten Mono- oder Diaminopyridins werden nach 12 h Meßzeit in dem Gerät freigesetzt.

13. Pharmazeutische Formulierung nach Anspruch 11, die eine Auflösungsgeschwindigkeit aufweist, die beim Messen in einem Löseapparat vom Typ II nach der U.S.-Pharmacopoeia XXII in Wasser und bei 50 U/min im wesentlichen dem folgenden Auflösungsmuster entspricht:

a) 10 bis 40 % des gesamten Mono- oder Diaminopyridins werden nach 1 h Meßzeit in dem Gerät freigesetzt;

b) 25 bis 65 % des gesamten Mono- oder Diaminopyridins werden nach 4 h Meßzeit in dem Gerät freigesetzt;

c) 40 bis 80 % des gesamten Mono- oder Diaminopyridins werden nach 8 h Meßzeit in dem Gerät freigesetzt;

d) 50 bis 90 % des gesamten Mono- oder Diaminopyridins werden nach 12 h Meßzeit in dem Gerät freigesetzt; und

f) nicht weniger als 75 % des gesamten Mono- oder Diaminopyridins werden nach 24 h Meßzeit in dem Gerät freigesetzt.

14. Pharmazeutische Formulierung nach Anspruch 11, die eine Auflösungsgeschwindigkeit aufweist, die beim Messen in einem Löseapparat vom Typ II nach der U.S.-Pharmacopoeia XXII in Wasser und bei 50 U/min im wesentlichen dem folgenden Auflösungsmuster entspricht:

a) 20 bis 50 % des gesamten Mono- oder Diaminopyridins werden nach 1 h Meßzeit in dem Gerät freigesetzt;

b) 30 bis 70 % des gesamten Mono- oder Diaminopyridins werden nach 4 h Meßzeit in dem Gerät freigesetzt;

c) 40 bis 80 % des gesamten Mono- oder Diaminopyridins werden nach 8 h Meßzeit in dem Gerät freigesetzt; und

d) nicht weniger als 75 % des gesamten Mono- oder Diaminopyridins werden nach 12 h Meßzeit in dem Gerät freigesetzt.

15. Pharmazeutische Formulierung nach einem der Ansprüche 11 bis 14, die eine Mischung von Pellets nach einem der Ansprüche 2 bis 9 zusammen mit bis zu 60 Gew.-% der schnell freisetzenden Form von Mono- oder Diaminopyridin, insbesondere schnell freisetzende Pellets, enthält.

16. Pharmazeutische Formulierung nach Anspruch 15, wobei die schnell freisetzenden Pellets folgendes enthalten: einen Kern aus Mono- oder Diaminopyridin-Wirkstoff oder einem pharmazeutisch verträglichen Salz hiervon in Verbindung mit einem oder mehreren pharmazeutisch verträglichen Hilfsstoff(en), wobei die Mono- oder Diaminopyridin-Komponente und der(die) pharmazeutisch verträgliche(n) Hilfsstoff(e) in einem Verhältnis von 1:10 bis 1:20 vorhanden sind, und eine mehrschichtige Membran, die den Kern umgibt und als Hauptteil ein pharmazeutisch verträgliches, filmbildendes, wasserlösliches Polymeres und gegebenenfalls einen kleineren Teil eines pharmazeutisch verträglichen, filmbildenden, wasserunlöslichen Polymeren enthält, wobei die Anzahl der Schichten in der Membran und das Verhältnis von wasserlöslichem Polymeren zu wasserunlöslichem Polymeren wirksam ist, um eine relativ unmittelbare Freisetzung des Wirkstoffes aus dem Pellet zu ermöglichen.

17. Pharmazeutische Formulierung nach Anspruch 15, wobei die Pellets eine Auflösungsgeschwindigkeit besitzen, die beim Messen *in vitro* in einem Löseapparat vom Typ II nach der U.S.-Pharmacopoeia XXII in Wasser bei 50 U/min im wesentlichen dem folgenden Auflösungsmuster entspricht:

    a) nicht weniger als 70 % des gesamten Mono- oder Diaminopyridins werden nach 1 h Meßzeit in dem Gerät freigesetzt; und

    b) nicht weniger als 85 % des gesamten Mono- oder Diaminopyridins werden nach 2 h Meßzeit in dem Gerät freigesetzt.

18. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 9 oder 11 bis 17, woraus der Mono- oder Diaminopyridin-Wirkstoff mit einer Geschwindigkeit freigesetzt wird, die die kontrollierte Absorption hiervon während eines Zeitraums von 24 h nach der oralen Verabreichung gestattet, wobei die Geschwindigkeit *in vivo* gemessen wird und eine T_{max} zwischen 2 und 16 h aufweist und die minimalen wirksamen Blutkonzentrationen nach 12 bis 20 h während eines Zeitraums von 24 h erreicht werden.

19. Verwendung eines Mono- oder Diaminopyridin-Wirkstoffes zur Herstellung eines Medikaments zur Verwendung bei der Behandlung einer Krankheit des Nervensystems, die durch eine Verlangsamung der Nervenreiz-Weiterleitung gekennzeichnet ist, wobei das Medikament wirksam ist, um den Wirkstoff so freizusetzen, durch die bei einer Verabreichung auf ein- oder zweimal täglicher Basis therapeutisch wirksame Blutkonzentrationen während eines Zeitraums von 12 bis 24 h erzielt werden.

20. Verwendung nach Anspruch 19, wobei die Krankheit des Nervensystems durch eine Entmarkung des Zentralnervensystems, insbesondere durch Multiple Sklerose gekennzeichnet ist.

21. Verwendung nach Anspruch 19, wobei die Krankheit des Nervensystems Alzheimer Krankheit ist.

22. Verwendung nach einem der Ansprüche 9 bis 21, wobei das Medikament an ein Individuum in einer Dosis und für eine Dauer verabreicht wird, die für eine Toleranz der Dosis durch das Individuum ohne Anzeichen von Nebenwirkungen ausreichen, und wobei anschließend die Dosis des Wirkstoffes in ausgewählten Zeitabständen gesteigert wird, bis eine therapeutische Dosis erreicht ist.

23. Verwendung nach Anspruch 22, wobei zu Beginn der Behandlung der Wirkstoff in einer Dosis von weniger als 15 mg/Tag verabreicht wird, bis ein Toleranz-Zustand erreicht ist.

24. Verwendung nach Anspruch 23, wobei nach Erreichen des Toleranz-Zustand die verabreichte Dosis um Mengen von wenigstens 5-15 mg/Tag gesteigert wird, bis die therapeutische Dosis erreicht ist.

Revendications

1. Formulation pharmaceutique comprenant une mono- ou diaminopyridine, destinée à l'administration par voie orale à raison d'une ou deux prises par jour, ladite formulation comprenant ledit agent actif à base de mono- ou diaminopyridine dans un véhicule polymère capable de libérer ladite mono- ou diaminopyridine à une vitesse permettant l'absorption contrôlée de celle-ci en une durée qui n'est pas inférieure, en moyenne, à 12 heures et à une vitesse suffisante pour produire des taux sanguins thérapeutiquement efficaces pendant une durée de 12-24 heures après administration par voie orale, ladite vitesse étant mesurée *in vitro* comme la vitesse de dissolution de ladite formulation, mesurée dans un dispositif de dissolution de type II selon la Pharmacopée U.S. XXII, dans de l'eau, à 50 tours par minute, correspondant essentiellement au schéma suivant :

    a) pas plus de 50 % de la teneur totale en mono- ou diaminopyridine sont libérés après 1 heure de mesure dans ledit dispositif ;

    b) pas plus de 75 % de la teneur totale en mono- ou diaminopyridine sont libérés après 4 heures de mesure dans ledit dispositif ; et

    c) 100 % de la teneur totale en mono- ou diaminopyridine sont libérés en pas moins de 8 heures de mesure dans ledit dispositif.

2. Formulation pharmaceutique selon la revendication 1, qui comprend des granules destinés à l'administration par voie orale, lesdits granules étant constitués par un noyau de mono- ou diaminopyridine ou d'un sel pharmaceutiquement acceptable de celle-ci, en association avec un ou plusieurs excipients pharmaceutiquement acceptables, le composant mono- ou diaminopyridine et le ou les excipients pharmaceutiquement acceptables étant présents dans un rapport de 10:1 à 1:20, et une membrane multicouche entourant ledit noyau et contenant une proportion prépondérante d'un polymère filmogène insoluble dans l'eau, pharmaceutiquement acceptable, et éventuellement une proportion mineure d'un polymère filmogène hydrosoluble, pharmaceutiquement acceptable, le nombre de couches de ladite membrane et le rapport dudit polymère

hydrosoluble audit polymère insoluble dans l'eau, lorsque ledit polymère hydrosoluble est présent, étant ajustés de façon à libérer ladite mono- ou diaminopyridine dudit granule à une vitesse permettant l'absorption contrôlée de celle-ci en une durée qui n'est pas inférieure, en moyenne, à 12 heures après administration par voie orale, ladite vitesse étant mesurée *in vitro* comme la vitesse de dissolution dudit granule, mesurée dans un dispositif de dissolution de type II selon la Pharmacopée U.S. XXII, dans de l'eau, à 50 tours par minute, correspondant essentiellement au schéma suivant :

a) pas plus de 50 % de la teneur totale en mono- ou diaminopyridine sont libérés après 1 heure de mesure dans ledit dispositif ;

b) pas plus de 75 % de la teneur totale en mono- ou diaminopyridine sont libérés après 4 heures de mesure dans ledit dispositif ; et

c) 100 % de la teneur totale en mono- ou diaminopyridine sont libérés en pas moins de 8 heures de mesure dans ledit dispositif.

3. Formulation pharmaceutique selon la revendication 2, dans laquelle la libération de la mono- ou diaminopyridine à partir dudit granule est réalisée à une vitesse permettant l'absorption contrôlée de celle-ci en une durée de 24 heures après administration par voie orale, ladite vitesse étant mesurée dans un dispositif de dissolution de type II selon la Pharmacopée U.S. XXII, dans de l'eau, à 50 tours par minute, ce qui correspond essentiellement au schéma de dissolution suivant :

a) de 0 à 40 % de la teneur totale en mono- ou diaminopyridine sont libérés après 1 heure de mesure dans ledit dispositif ;

b) de 20 à 60 % de la teneur totale en mono- ou diaminopyridine sont libérés après 4 heures de mesure dans ledit dispositif ;

c) de 30 à 80 % de la teneur totale en mono- ou diaminopyridine sont libérés après 8 heures de mesure dans ledit dispositif ;

d) de 50 à 90 % de la teneur totale en mono- ou diaminopyridine sont libérés après 12 heures de mesure dans ledit dispositif ;

e) pas moins de 75 % de la teneur totale en mono- ou diaminopyridine sont libérés après 24 heures de mesure dans ledit dispositif.

4. Formulation pharmaceutique selon la revendication 2, dans laquelle la libération de la mono- ou diaminopyridine à partir dudit granule est réalisée à une vitesse permettant l'absorption contrôlée de celle-ci en une durée de 12 heures après administration par voie orale, ladite vitesse étant mesurée dans un dispositif de dissolution de type II selon la Pharmacopée U.S. XXII, dans de l'eau, à 50 tours par minute, ce qui correspond essentiellement au schéma de dissolution suivant :

a) de 0 à 40 % de la teneur totale en mono- ou diaminopyridine sont libérés après 1 heure de mesure dans ledit dispositif ;

b) de 20 à 60 % de la teneur totale en mono- ou diaminopyridine sont libérés après 4 heures de mesure dans ledit dispositif ;

c) de 30 à 80 % de la teneur totale en mono- ou diaminopyridine sont libérés après 8 heures de mesure dans ledit dispositif ;

d) pas moins de 75 % de la teneur totale sont libérés après 12 heures de mesure dans ledit dispositif.

5. Formulation pharmaceutique selon l'une quelconque des revendications 2 à 4, dans laquelle le noyau comprend :

a) un mélange en poudre contenant une mono- ou diaminopyridine ou un sel pharmaceutiquement acceptable de celle-ci et un excipient pharmaceutiquement acceptable, et

b) une substance polymère contenant une proportion prépondérante d'un polymère hydrosoluble, pharmaceutiquement acceptable, et une proportion mineure d'un polymère insoluble dans l'eau, pharmaceutiquement acceptable,

ledit noyau comprenant des couches dudit mélange en poudre et de ladite substance polymère superposées les unes sur les autres et ladite substance polymère étant présente en une quantité suffisante pour assurer que la totalité dudit mélange en poudre est appliquée sur ledit noyau.

6. Formulation pharmaceutique selon l'une quelconque des revendications 2 à 5, dans laquelle le polymère hydrosoluble du noyau ou de la membrane est identique ou différent et est choisi parmi le poly(alcool vinylique), la polyvinylpyrrolidone, la méthylcellulose, l'hydroxypropylcellulose l'hydroxypropylméthylcellulose, l'agar, le carraghenan, le xanthane ou le polyéthylèneglycol, ou des mélanges de ces composés.

7. Formulation pharmaceutique selon l'une quelcon-

que des revendications 2 à 5, dans laquelle le polymère hydrosoluble du noyau ou de la membrane est remplacé par une substance polymère qui est totalement perméable à la mono- ou diaminopyridine et à l'eau et comprend un copolymère d'esters d'acide acrylique ou méthacrylique.

8. Formulation pharmaceutique selon l'une quelconque des revendications 2 à 7, dans laquelle le polymère insoluble dans l'eau du noyau ou de la membrane est choisi parmi l'éthylcellulose, l'acétate de cellulose, le propionate de cellulose (de poids moléculaire faible, moyen ou élevé), l'acétate-propionate de cellulose, l'acétate-butyrate de cellulose, l'acétate-phtalate de cellulose, le triacétate de cellulose, le poly(méthacrylate de méthyle), le poly(méthacrylate d'éthyle), le poly(méthacrylate de butyle), le poly(méthacrylate d'isobutyle), le poly(méthacrylate d'hexyle), le poly(méthacrylate d'isodécyle), le poly(méthacrylate de lauryle), le poly(méthacrylate de phényle), le poly(acrylate de méthyle), le poly(acrylate d'isopropyle), le poly(acrylate d'isobutyle), le poly(acrylate d'octadécyle), le polyéthylène, le polyéthylène basse densité, le polyéthylène haute densité, le polypropylène, le poly(oxyde d'éthylène), le poly(téréphtalate d'éthylène), le poly(vinylisobutyléther), le poly(acétate de vinyle), le poly(chlorure de vinyle), le polyuréthane ou un mélange de ces composés ou un polymère naturel choisi parmi le shellac, le chitosan, la gomme de genévrier ou un de leurs mélanges.

9. Formulation pharmaceutique selon l'une quelconque des revendications 2 à 8, dans laquelle le polymère insoluble dans l'eau du noyau ou de la membrane est remplacé par une substance polymère qui est légèrement perméable à la mono- ou diaminopyridine et à l'eau et comprend un copolymère d'esters d'acide acrylique ou méthacrylique.

10. Procédé de préparation d'une formulation pharmaceutique selon l'une quelconque des revendications 2 à 9, comprenant les étapes consistant à former un noyau de mono- ou diaminopyridine ou d'un sel pharmaceutiquement acceptable de celle-ci, et un ou plusieurs excipients pharmaceutiquement acceptables et à enrober le noyau avec une membrane en un polymère filmogène ou un mélange de celui-ci selon la revendication 2, qui permet la libération de la mono- ou diaminopyridine ou du sel pharmaceutiquement acceptable de celle-ci conformément à l'une quelconque des revendications 2 à 4.

11. Formulation pharmaceutique comprenant des granules selon l'une quelconque des revendications 2 à 9, ladite formulation comprenant une quantité suffisante d'une forme à libération rapide de mono- ou diaminopyridine pour assurer immédiatement des taux sanguins thérapeutiquement efficaces conjointement avec des taux sanguins thérapeutiquement efficaces sur une période de 12 à 24 heures suivant chaque administration par voie orale.

12. Formulation pharmaceutique selon la revendication 11, qui présente une vitesse de dissolution, mesurée dans un dispositif de dissolution de type II selon la Pharmacopée U.S. XXII, dans de l'eau, à 50 tours par minute, correspondant essentiellement au schéma de dissolution suivant :

a) de 20 à 60 % de la teneur totale en mono- ou diaminopyridine sont libérés après 2 heures de mesure dans ledit dispositif ;

b) de 30 à 70 % de la teneur totale en mono- ou diaminopyridine sont libérés après 4 heures de mesure dans ledit dispositif ;

c) de 50 à 90 % de la teneur totale en mono- ou diaminopyridine sont libérés après 8 heures de mesure dans ledit dispositif ; et

d) pas moins de 75 % de la teneur totale en mono- ou diaminopyridine sont libérés après 12 heures de mesure dans ledit dispositif.

13. Formulation pharmaceutique selon la revendication 11, qui présente une vitesse de dissolution, mesurée dans un dispositif de dissolution de type II selon la Pharmacopée U.S. XXII, dans de l'eau, à 50 tours par minute, correspondant essentiellement au schéma de dissolution suivant :

a) de 10 à 40 % de la teneur totale en mono- ou diaminopyridine sont libérés après 1 heure de mesure dans ledit dispositif ;

b) de 25 à 65 % de la teneur totale en mono- ou diaminopyridine sont libérés après 4 heures de mesure dans ledit dispositif ;

c) de 40 à 80 % de la teneur totale en mono- ou diaminopyridine sont libérés après 8 heures de mesure dans ledit dispositif ;

d) de 50 à 90 % de la teneur totale en mono- ou diaminopyridine sont libérés après 12 heures de mesure dans ledit dispositif ; et

e) pas moins de 75 % de la teneur totale en mono- ou diaminopyridine sont libérés après 24 heures de mesure dans ledit dispositif.

14. Formulation pharmaceutique selon la revendication

11, qui présente une vitesse de dissolution, mesurée dans un dispositif de dissolution de type II selon la Pharmacopée U.S. XXII, dans de l'eau, à 50 tours par minute, correspondant essentiellement au schéma de dissolution suivant :

a) de 20 à 50 % de la teneur totale en mono- ou diaminopyridine sont libérés après 1 heure de mesure dans ledit dispositif ;

b) de 30 à 70 % de la teneur totale en mono- ou diaminopyridine sont libérés après 4 heures de mesure dans ledit dispositif ;

c) de 40 à 80 % de la teneur totale en mono- ou diaminopyridine sont libérés après 8 heures de mesure dans ledit dispositif ; et

d) pas moins de 75 % de la teneur totale en mono- ou diaminopyridine sont libérés après 12 heures de mesure dans ledit dispositif.

15. Formulation pharmaceutique selon l'une quelconque des revendications 11 à 14, qui comprend un mélange de granules selon l'une quelconque des revendications 2 à 9, conjointement avec jusqu'à 60 % en poids de ladite forme à libération rapide de mono- ou diaminopyridine, en particulier des granules à libération rapide.

16. Formulation pharmaceutique selon la revendication 15, dans laquelle les granules à libération rapide comprennent un noyau formé d'un agent actif à base de mono- ou diaminopyridine ou d'un sel pharmaceutiquement acceptable de celle-ci, en association avec un ou plusieurs excipients pharmaceutiquement acceptables, le composant à base de mono- ou diaminopyridine et le ou les excipients pharmaceutiquement acceptables étant présents dans un rapport de 10:1 à 1:20, et une membrane multicouche entourant ledit noyau et contenant une proportion prépondérante d'un polymère filmogène hydrosoluble, pharmaceutiquement acceptable, et éventuellement une proportion mineure d'un polymère filmogène insoluble dans l'eau, pharmaceutiquement acceptable, le nombre de couches de ladite membrane et le rapport dudit polymère hydrosoluble audit polymère insoluble dans l'eau étant ajustés de façon à libérer presque immédiatement l'agent actif dudit granule.

17. Formulation pharmaceutique selon la revendication 16, dans laquelle les granules ont une vitesse de dissolution, mesurée *in vitro* dans un dispositif de dissolution de type II selon la Pharmacopée U.S. XXII, dans de l'eau, à 50 tours par minute, qui correspond essentiellement au schéma de dissolution suivant :

a) pas moins de 70 % de la teneur totale en mono- ou diaminopyridine sont libérés après 1 heure de mesure dans ledit dispositif ; et

b) pas moins de 85 % de la teneur totale en mono- ou diaminopyridine sont libérés après 2 heures de mesure dans ledit dispositif.

18. Formulation pharmaceutique selon l'une quelconque des revendications 1-9 ou 11-17, à partir de laquelle l'agent actif mono- ou diaminopyridine est libéré à une vitesse permettant une absorption contrôlée de celle-ci en une durée de vingt quatre heures suivant l'administration par voie orale, ladite vitesse étant mesurée *in vivo* et ayant un Tmax compris entre 2 et 16 heures et produisant des taux sanguins efficaces minimaux de 12 à 20 heures pendant une durée de 24 heures.

19. Utilisation d'un agent actif à base de mono- ou diaminopyridine pour la fabrication d'un médicament destiné à être utilisé dans le traitement d'une maladie neurologique caractérisée par un ralentissement de la transmission des impulsions nerveuses, dans laquelle ledit médicament est capable de libérer ledit agent actif de manière à produire des taux sanguins thérapeutiquement efficaces sur une période de 12-24 heures dans le cas d'une administration une ou deux fois par jour.

20. Utilisation selon la revendication 19, dans laquelle la maladie neurologique est caractérisée par une démyélination du système nerveux central, en particulier la sclérose en plaques.

21. Utilisation selon la revendication 19, dans laquelle la maladie neurologique est la maladie d'Alzheimer.

22. Utilisation selon l'une quelconque des revendications 19-21, dans laquelle ledit médicament est administré à un sujet à une dose et pendant une durée suffisantes pour permettre audit sujet de tolérer ladite dose sans présenter d'effet adverse et ensuite, la dose dudit agent actif est augmentée à des intervalles déterminés jusqu'à ce que la dose thérapeutique soit atteinte.

23. Utilisation selon la revendication 22, dans laquelle au début du traitement l'agent actif est administré à une dose inférieure à 15 mg/jour jusqu'à ce qu'un état tolérable soit atteint.

24. Utilisation selon la revendication 23, dans laquelle, lorsque ledit état tolérable est atteint, la dose administrée est augmentée par quantités d'au moins 5-15 mg/jour jusqu'à ce que ladite dose thérapeutique soit atteinte.